REMARKS

Claims 1 - 129 are pending in the application. No claims have been amended. No new claims have been added. Claims 2 – 4, 6, 8 – 11, 16, 19, 20, 22 - 129 have been previously cancelled. No new matter has been added by virtue of these amendments; support therefore can be found in throughout the specification and original claims of the application.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 1, 3 – 5, 7, 12 – 15 and 17 Under 35 USC 103(a)

The Examiner has maintained the rejection to claims 1, 3 – 5, 7 12 – 15 and 17 under 35 USC 103(a) as being unpatentable over Dominguez et al. (J of Immunological Methods, 1998, 220: 115 – 221) in view of Hooper et al. (USPN 6, 451, 309; the '309 reference herein). Applicants respectfully traverse the rejection.

The instant claims recite a method comprising incubating a mixture comprising at least one cell, a labeled invasin that encodes a detectable label, wherein the labeled invasin is a virus, and a candidate agent under conditions wherein the labeled invasin can invade the cell; and detecting the detectable label within the cell, wherein a decrease of detectable label in the cell due to the candidate agent indicates that the candidate agent decreases invasion of the cell by the invasin.

The Examiner argues that the Dominguez reference "discloses "GFP expressed by a recombinant vaccinia virus that permits early detection of infected cells by flow cytometry (and) uses the construct as an infection tag and teaches that it is useful for studying tropism in a complex cell population such as porcine PMBCs." (Office Action, p.3). The Examiner admits that the Dominguez reference "does not disclose the use of the construct for testing the anti-viral activity of candidate agents, particularly antibodies." (Office Action, p.3). The Examiner argues that the '309 reference "teaches

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the production and identification of vaccinia monoclonal antibodies for the purpose pf therapeutic treatment (passive immunization) of vaccinia in humans (and) discloses that potential targets for poxvirus therapeutics, monoclonal antibodies, were generated in mice and tested for their ability to neutralize virus and protect mice from challenge," (Office Action, p.3). The Examiner argues that "(i)t would have been obvious to use the vaccinia-GFP construct of Dominguez to test the infectivity of cells in the presence of...the monoclonal antibodies to determine whether the antibodies are effective agents that inhibit vaccinia virus infectivity." (Office Action, p.4). Applicants disagree.

The Dominguez reference teaches the construction of recombinant vaccinia expressing GFP for detection of cells by flow cytometry. However, and as pointed out by the Examiner on page 3 of the Office Action, the construct as taught by Dominguez, is merely used "as **an infection tag**" and "is useful for studying tropism." As pointed out by the Examiner, the Dominguez reference does not teach the features of the invention as claimed. In particular, the Dominguez reference "does not disclose the use of the construct for testing the anti-viral activity of candidate agents, particularly antibodies." (Office Action, p.3).

The Examiner argues that the '309 reference "teaches the production and identification of vaccinia monoclonal antibodies for the purpose of therapeutic treatment (passive immunization) of vaccinia in humans...and discloses that potential targets for poxvirus therapeutics, monoclonal antibodies, were generated in mice and tested for their ability to neutralize virus and protect mice from challenge." (Office Action, p.3).

The '309 reference (Hooper) does not cure the flaws of the Dominguez reference. No combination of Dominguez and the '309 reference teaches the method as instantly claimed, in particular a method to measure protection of cells against virus invasion by measuring a decrease in invasion by a candidate agent.

The present application is directed to the development of a novel assay to measure protection of cells against virus invasion. As taught in the specification, the method as claimed is the only validated alternative method to the classical labor intensive Plaque Reduction Assay (PRNT).

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The methods of the present Application provide a **quantitative** determination of invasion and a **prediction of virus lethality**, neither of which are possible with the methods taught by either Dominguez or Hooper alone, or in combination.

The present specification teaches an ELISA assay that enables quantitative determination of virus infectivity based on a readout measured against a standard curve, for example as taught at page 9 of the specification, and in Example I:

> The novel methods described herein may be used to replace the traditional PRNT assays. For example, it has been demonstrated that the beta-Gal reporter gene assay, using a recombinant vaccinia virus vSC56, is rapid (24 hr), sensitive, reproducible, and produces very similar results to those obtained in two different PRNT assays. Since the readout is an enzymatic reaction resulting in a substrate color change, it can be read by an ELISA reader instrument currently available in most clinical laboratories. (page 9).

Further, Applicants have shown that the in vitro neutralization assays are predictive of lethality, for example at page 10 of the specification, and in Example III. .

> In order to further establish the in vivo biological correlation of the in vitro neutralization assays of the invention, a mouse lethality model using SCID mice has been established. The difference in neutralization titer observed in the beta-Gal assay correlated positively with significant difference in the protective efficiency against lethal infection of SCID mice with vaccinia (Wyeth). (page 10, line 21 – 28).

Neither the Dominguez reference or the '309 reference, alone or in combination, teaches or suggests a method that can provide a **quantitative** determination of invasion or a prediction of virus **lethality**.

As pointed out by the Examiner, "it would have been obvious to use the vaccinia-GFP construct of Dominguez **to test the infectivity** of cells in the presence of (the '309 reference's) monoclonal antibodies to determine whether the antibodies are effective agents that inhibit vaccinia virus infectivity." (Office Action, p.3; emphasis added). Dominguez merely teach "the usefulness of GFP as an infection marker" (p. 120), not as a marker that would be useful in providing a quantitative determination of invasion.

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Further, as pointed out by the Examiner, the '309 reference only teaches the production and potential activity of the monoclonal antibodies against vaccinia. The '309 reference does not teach or suggest a reporter-based- assay (for example, B-galactosidase vaccinia virus or GFP-expressing vaccinia) to demonstrate the protective activity of their monoclonal antibodies, nor does the '309 reference does not provide any method for quantitative determination.

Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejection of Claims 18 and 21 Under 35 USC 103(a)

The Examiner has maintained the rejection to claims 18 and 21 under 35 USC 103(a) as being unpatentable over Dominguez et al. (J of Immunological Methods, 1998, 220: 115 – 221) in view of Hooper et al. (USPN 6, 451, 309; the '309 reference herein) as applied to claims 1 and 17, above, and further in view of Englemayer et al. (The J of Immunology, 1999, 163: 6762 – 6768). Applicants respectfully traverse the rejection.

As set forth above, the combination of the Dominguez and the '309 reference fail to teach the invention as claimed. The Englemayer reference does not cure the flaws of the Dominguez and the '309 references.

No combination of the cited art teaches the method as instantly claimed, in particular a method to measure protection of cells against virus invasion by measuring a decrease in invasion by a candidate agent. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Early consideration and allowance of the application are earnestly solicited.

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